REMARKS

A Request for Continuing Examination is submitted herewith. Reconsideration of the above referenced application is respectfully requested. Upon entry of the foregoing amendment, Claims 72-87 will be pending. Claim 1 has been amended and Claims 1-71 and 88-95 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional application. No new matter has been introduced and entry of this amendment is respectfully requested.

Given the cancellation of Claims 88-95 which were pending in this case prior to filing of the Request for Continuing Examination, the responses provided herein are made with consideration of the currently pending claims.

A discussion of the present claims as they related to the July 20, 2006 Office Action in USSN 10/327,869 (from which the instant case claims priority) is provided below.

Rejection under 35 U.S.C. §112, first paragraph, enablement.

Claims 88-95 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action maintains that Claims 88-95 are directed to methods of treating cancer of the bladder by treating the luminal surface of the bladder with a composition comprising an oncolytic virus and a transduction enhancing agent. The Office Action further states that while being enabling for treating a superficial tumor in the luminal surface of the bladder with a transduction enhancing agent according to formulas I or II in Claim 88 and subsequently contacting the bladder with an oncolytic virus, the specification does not reasonably provide

enablement for treatment of cancer in the muscular layer of the bladder. The Office Action further states that the specification does not enable one of skill in the art to use the invention commensurate with the scope of the claims.

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without undue experimentation (e.g., In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir., 1991). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

In accordance with the accepted standards of enablement set forth above, an invention is enabled if one skilled in the art could make and use the claimed invention without undue experimentation.

Claims 88-95 have been cancelled herein, obviating the basis for rejection set forth in the outstanding Final Office Action dated May 12, 2006.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

Rejection under 35 U.S.C. §103(a).

In the Office Action, the Examiner sets forth a number of grounds for rejection under 35 USC §103, each of which is discussed in detail as they apply to the current claims, below.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. (Cancer Res. 62:3743-3750, 2002) in view of Heidrun et al. (US Patent 5,789,244).

On page 6 of the Office Action, Zhang et al. is cited as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel.

Heidrun et al. is cited as allegedly teaching methods of treating bladder cancer by intravesical administration of adenoviral vectors and that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

On page 6, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Zhang et al. by applying adenovirus to the luminal surface of the bladder as taught by Heidrun et al. The Office Action states that it would have been obvious to use the method in vivo, and one would have been motivated to use luminal delivery in order to improve access to tumors in the bladder epithelium.

Applicants respectfully disagree.

As stated in MPEP §2142, the examiner bears the initial burden of factually supporting a prima facie conclusion of obviousness. The examiner must show that the claimed invention was obvious to a person of ordinary skill in the art at the time the application was filed. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art

reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Claims 88-95 have been cancelled herein, obviating the basis for rejection set forth in the outstanding Final Office Action dated May 12, 2006.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Heidrun et al. (US Patent 5,789,244) and Mullen et al. (Oncologist 7:106-119, 2002).

Watanabe et al. is cited as allegedly teaching methods of treating bladder cancer with replication deficient adenovirus carrying a suicide gene (ras) in a mouse model of bladder cancer, that the virus was instilled intravesically and inhibited the growth of superficial tumors.

The Office Action states that Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

Heidrun et al. is relied upon as teaching that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

Mullen et al. is cited as allegedly teaching that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication defective gene therapy vectors because the virus amplifies itself through several rounds of replication allowing an increase in gene expression leading to an amplified anti tumor effect.

On page 8 and 9, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Watanabe et al. by treating mouse bladders with sodium lauryl sulfate and to substitute replication competent adenoviruses for replication defective ones.

Claims 88-95 have been cancelled herein, obviating the basis for rejection set forth in the outstanding Final Office Action dated May 12, 2006.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 88-95 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. (Cancer Res. 62:3743-3750, 2002) in view of Heidrun et al. (US Patent 5,789,244) and Gaffar et al. (US Patent 5,368,844).

On page 10 of the Office Action, Zhang et al. is cited as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors

when administered at 3.33×10^9 pfu in combination with docetaxel. Page 10 of the Office Action further states that Zhang et al. do not teach administration to the luminal surface of the bladder or the use of a transduction enhancing agent that was an alkyl sulfate salt.

On page 10 of the Office Action, Heidrun et al. is cited as allegedly teaching methods of treating bladder cancer by intravesical administration of adenoviral vectors and that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycoaminoglycal layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate.

Gaffar is cited as allegedly teaching that sodium lauryl sulfate and sodium dodecyl benzene sulfonate are anionic surfactants with similar performance characteristics.

On page 10 and 11, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Zhang et al. by applying the adenovirus to the luminal surface of the bladder, as taught by Heidrun, in order to treat bladder cancer. The Office Action further states that it would have been obvious to modify the method of Zhang et al. by treating mouse bladders with sodium lauryl sulfate or sodium dodecyl benzene sulfonate in order to improve access to tumors in the bladder epithelium.

Claims 88-95 have been cancelled herein, obviating the basis for rejection set forth in the outstanding Final Office Action dated May 12, 2006.

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

The Present Claims As They Related To The Outstanding Office Action In USSN 10/327,869

With respect to the current claims, one of ordinary skill in the art would be informed by the teachings of the subject specification, as to how to make an oncolytic adenovirus composition comprising a urothelium-specific promoter. Urothelium specific promoters were known in the art at the time the application was filed, as evidenced by US Patent Publication No. 20020120117, published August 29, 2002. Hence, examples of urothelium specific promoters were known in the art and need not be further described in the specification.

Conner et al., was cited in corresponding USSN 10/327,869 as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside. In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent to enhance adenoviral transduction of the bladder epithelium. As indicated on page 41, lines 4-5 of the specification, n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction.

Amiel et al. was also cited in corresponding USSN 10/327,869, as allegedly teaching directed to a method of decellularizing a biological matrix by: (a) obtaining a tissue of interest and (b) treating the tissue of interest with a decellularization solution containing a cell lysis reagent such as a non-ionic detergent, to obtain an acellular biological matrix. Amiel et al. lists non-ionic detergent including TWEEN 20, TWEEN 40, TWEEN 80, sucrose monolaurate, N-octyl beta-D-glucopyranoside(OGP), lauryl maltoside (DDM) and others.

Ramesh et al., Identification of Pretreatment Agents to Enhance Adenovirus Infection of Bladder Epithelium, Mol. Ther. 10(4):697-705, 2004, describe the use of conditionally replication-competent oncolytic adenoviruses for intravesicular therapy of bladder cancer. The reference shows that a class of compounds has been identified that is effective for pretreatment of bladder urothelium, permitting efficient adenoviral infection, by "permeabilizing" (not

dissolving) a "mucus" membrane composed of the GAG layer, which is not a cell membrane. The tight junctions between the basal-lateral surfaces of adjacent cells lining the urothelium and the GAG layer underlying the urothelium make it difficult to penetrate (p697 of Ramesh et al). The "GAG layer" is a complex set of proteoglycans and glycoproteins on the bladder surface. The transduction enhancing agents of the invention allow access of adenovirus to the cells below the GAG layer. The function of the transduction enhancing agents of the invention is not cell membrane solublization (as described in a number of references cited by the Examiner in USSN 10/327,869). The detergents disclosed in the cited references are intended to solublize membranes, not permeabilize the complex set of proteoglycans and glycoproteins on the bladder surface which constitute the "GAG layer. It follows that not all detergents are effective as transduction enhancing agents and therefore would not be useful in the methods of the invention. One of skill in the art would appreciate that the effectiveness of a detergent in lysing a cell is not predictive of the effectiveness of that same detergent in enhancing bladder transduction.

For example, in USSN 10/327,869, the Examiner relies on Sedzik et al. as allegedly teaching dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside and heptyl-beta-D-thioglucopyranoside as detergents with performance characteristics similar to octyl-beta-D-glucopyranoside for solublizing PNS myelin membrane proteins.

Many detergents that lyse cell membranes and have been used for that purpose were screened and several reported on in Ramesh et al. Table 1 on page 698 of Ramesh et al., shows that many were not effective as transduction enhancers. For example, n-dodecyl-beta-D-maltoside and n-dodecyl-alpha-D-maltoside (disaccharides with a C12 side chain), sucrose monolaurate (C12) and 6-cyclohexyl hexyl-beta-D-maltoside (C12) as well as sodium dodecyl

sulfate (C12) were very effective transduction enhancing agents. In contrast, n-decyl-beta-D-maltoside (C10), n-octyl-beta-D-maltoside (C8), sodium decyl sulfate (C10) and sodium octyl sulfate (C8) were not effective as transduction enhancing agents.

Therefore the relevant art does not teach or suggest that cell membrane dissolving detergents common in the art would be effective at GAG layer permeabilization and tight junction splitting for enhancement of bladder urothelial transduction. Furthermore, the data in the instant specification (page 41, lines 4-5) indicates that n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction, while treatment of the bladder epithelium with dodecyl-beta-D-maltoside and 6-cyclohexyl hexyl-beta-D-maltoside resulted in a high level of transduction (page 37, line 24 through page 38, line 1).

The use of octyl-beta-D-glucopyranoside as taught by Conner et al. is inconsistent with the teachings of the specification of the instant application as stated above. Furthermore, the data provided above shows that the effectiveness of a particular monosaccharide as a transduction enhancing agent is not predictive of the effectiveness of the corresponding disaccharide. It follows that the instant application teaches that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with disaccharide transduction enhancing agents having a lipophillic side chain of a particular length, but not when treated with a disaccharide having a lipophillic side chain of 10 or fewer carbons or a monosaccharide as taught by Conner et al. Hence one of skill in the art, relying on Conner et al. and the other references cited in USSN 10/327,869 would not have a reasonable expectation of success in practicing the present invention

Conclusion

In light of the above, Applicants submit that this application is now in condition for allowance and therefore request favorable consideration. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants' counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

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